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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CHEN, STACY BROWN	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 10/27/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/787,181	YAMADA ET AL.	
	Examiner	Art Unit	
	Stacy B Chen	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *10-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☒ Claim(s) *2-9* is/are objected to.

8)☐ Claim(s) ___ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 October 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/21/2002*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election of Group I, claims 1-9, in the reply filed on August 30, 2004 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Specification

2. The specification is objected to for the following informalities:

- Page 7, lines 6 and 12 contain a typo with regard to "CAS".
- Page 11, line 17, has a word that is not clearly printed.
- Page 20, lines 17, 27 and 31 contain numbers that require corrected spacing and proper notation. For example, "(20 1)", is not properly notated.

Claim Objections

3. Claims 2-9 are objected to for the following informality: Claim 2 and depending claims 3-9 refer to "the substituted or unsubstituted sugar residue directly linked to the presenegenin skeleton". While the Office recognizes that the sugar residue is directly linked to the presenegenin skeleton, the claim from which claim 2 depends, claim 1, does not recite a sugar residue "directly linked" to the presenegenin skeleton. Although the Office understands the meaning of the claim, the claim should be amended to correct the lack of antecedent basis.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1, and dependent claims 2-9, recite the following phrase:

...where the substituted sugar residue essentially comprises an apiose residue as its substituent when the substituted sugar residue is tetrasubstituted.

It is unclear what is meant by "essentially comprises". The specification does not define how a sugar residue essentially comprises an apiose reside as its substituent. Claim 5, (a), recites a compound that is tetrasubstituted, however, the compound only has one apiose residue and three non-apiose residues. The claim language of claim 1 leads one to have apiose residues as all four substituents, however, the later claims (claim 5, (a)) do not support such an interpretation. Claim 1 indicates that the tetrasubstituted sugar residue "essentially comprises" an apiose residue. The transitional phrase, "comprising", indicates open claim language. The transitional phrases, "consisting" and "consisting essentially of", are closed claim language. However, Applicant's use of "essentially comprising" is unclear. The Office has interpreted the claims as "comprising".

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 9 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a vaccine preparation for influenza, rotavirus, measles virus, rubella virus, mumps virus, *Bordetella pertussis*, and diphtheria bacillus, does not reasonably provide enablement for a vaccine preparation for *Helicobacter pylori*, enterohaemorrhagic *E. coli* (EHEC), *Chlamydia*, *Mycoplasma*, *plasmodium*, *coccidium* and schistosome. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. The breadth of the claims encompasses a vaccine for each of the microorganisms listed in claim 9. A vaccine is a preparation of killed or weakened microorganisms that induce a protective immune response in the recipient. The recipient is then protected upon subsequent challenge and disease is prevented. The claims encompass protective immunity against microorganisms for which there are no vaccines available. The nature of the invention is vaccination against pathogenic microorganisms (bacteria, viruses and parasites). The state of the art reveals that there are no vaccines available for the following pathogens: *Helicobacter pylori*, enterohaemorrhagic *E. coli* (EHEC), *Chlamydia*, *Mycoplasma*, *plasmodium*, *coccidium* and schistosomes. The following are cited as evidence of the lack of vaccines for these microorganisms:

- *Helicobacter pylori (H. pylori)*. Michetti (*Gut*, 1997, 41:728-730) discloses the advances and challenges in the search for a *H. pylori* vaccine. Current treatment is antibiotics and is in no way preventative. Vaccination of mice with the VacA cytotoxin and urease has shown protective responses, but the application to humans will require a

greater understanding of the type of immune response required for protection (page 729, first column, paragraphs 2 and 3).

- Enterohaemorrhagic *E. coli* (EHEC). Li *et al.* (*Infection and Immunity*, Sept. 2000, 68(9):5090-5095) disclose that there is currently no vaccine for EHEC (abstract). There is no good animal model for EHEC pathogenesis (page 5090, second column, beginning of last paragraph). Li *et al.* demonstrate that there is a strong immune response among human patients to the Tir virulence factor of EHEC, but there is not enough information for its use as a vaccine candidate yet (page 5094, last paragraph).
- *Chlamydia.* Lu *et al.* (*J. Immunol.* 2002, 169:6324-6331) disclose vaccination of mice with inactivated whole cell *C. trachomatis* (mouse pneumonitis, mouse model) in combination with GM-CSF as an adjuvant (abstract). Without the GM-CSF, the mice exhibited no protective response against challenge. However, with the adjuvant, mice exhibited enhanced cellular and humoral immune responses to homologous challenge. The findings of Lu *et al.* have implications on the development of a vaccine for humans.
- *Mycoplasma.* Mycoplasmas are currently treated with antibiotics, however, no vaccine currently exists for humans. Duffy *et al.* (*J. Antimicrobial Chemotherapy*, 2000, 45, Suppl. S1, pages 29-33) disclose antibiotic treatments for mycoplasmas, which is the current state of the art treatment.
- *Plasmodium.* The Centers for Disease Control (CDC) fact sheet about malaria, discloses that there is no vaccine approved for human use (page 3, "Preventing

Malaria" subheading) because the life cycle of the parasite is very complex, displaying different antigens at different times. Current treatment for parasites is drugs.

- *Coccidium.* The MayoClinic fact sheet on Toxoplasmosis (*Toxoplasma gondii*, an intestinal coccidium) discloses that the disease is treatable with drugs, but there is no vaccine (page 1, see "Overview").
- Schistosome. The CDC fact sheet about Schistosomiasis discloses that the parasitic infection is treatable with drugs, but there is no vaccine for the parasite because of its complex life cycle and varied antigen display.

The level of skill in the art regarding vaccination is high. The level of predictability in the art with regard to vaccination of viruses and bacteria is low because of the complexities of microorganisms and the human immune response. The amount of guidance in the specification is limited to a listing on pages 12-13 of bacterial and viral vaccines, some of which are enabled, and some of which are described generally in terms of antigens or whole cell/virus preparations. The amount of guidance provided for *mycoplasma*, HIV and *H. pylori* does not specifically teach which antigens are useful for vaccination. The working examples are drawn to influenza, pertussis-diphtheria-tetanus combined vaccine, Hepatitis B, measles, rubella and mumps (all recognized vaccines). Other working examples include Japanese encephalitis virus and *mycoplasma*, showing induction of an immune response. It would require undue experimentation to discover the antigens or cell/virus preparations required to induce a protective immune response for the claimed microorganisms *Helicobacter pylori*, enterohaemorrhagic *E. coli* (EHEC), *Chlamydia*, *Mycoplasma*, *plasmodium*, *coccidium* and schistosomes. Given the breadth of the claims, the nature of the invention, the state of the art, the high level of skill in the

art, the low level of predictability in the art, the limited guidance in the specification and working examples, and the undue amount of experimentation required to discover vaccine preparations of various microorganisms, the claims are not enabled for their full scope.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-6 are rejected under 35 U.S.C. 102(b) as being anticipated by Sakuma *et al.* (*Chem. Pharm. Bull.*, 1981, 30(3):810-821, herein, "Sakuma"). Claim 1 is drawn to an adjuvant comprising a saponin compound having a presenegenin skeleton substituted with a substituted or unsubstituted sugar residue at position 28, where the substituted sugar residue essentially comprises an apiose residue as its substituent when the substituted sugar residue is tetra-substituted. (The transition phrase, "essentially comprises", is unclear, see rejection under 35 U.S.C. 112, second paragraph above. The Office is interpreting the phrase as "comprising".) Specifically, the substituted or unsubstituted sugar residue is directly linked to the presenegenin skeleton at position 28, and is a sugar residue containing 3 or more carbon atoms, such as a substituted or unsubstituted fucose residue. Claim 4 is drawn to a specific structure (see claim 4) which has a presenegenin skeletal structure, with a sugar residue at position 28. Claim 5, embodiments (a)-(d) represent different substitutions on the sugar residues. Also claimed is the compound of claim 1, wherein the saponin compound is prepared from a crude drug. (The

specification gives an example of a crude drug, *Polygalae Radix,* extracted from the root of the plant, *Polygala tenuifolia* Willdenow, page 9, lines 15-22.)

Sakuma discloses onjisaponins A, B, C, D, E, F and G, which correspond to the claimed compounds and were prepared from a "crude drug", the root of *Polygala tenuifolia* Willdenow (abstract and page 2, chart 1). Onjisaponin A has a presenegenin skeletal structure and a tetra-substituted sugar residue having a monomethoxy cinnamate residue, a rhamnose residue, an apiose residue and a galactose residue. Sakuma also discloses onjisaponin E, which has a presenegenin skeletal structure and di-substituted sugar residue having a trimethoxycinnamate residue and a galactose residue. Onjisaponin F has a presenegenin skeletal structure and a tri-substituted sugar residue having a trimethoxycinnamate residue, an apiose residue and an arabinose residue. Onjisaponin G has a presenegenin skeletal structure and a di-substituted sugar residue having a trimethoxycinnamate residue and an apiose residue. Onjisaponins A, E, F and G read on claim 5 embodiments (a), (b), (c) and (d), respectively. While the adjuvant properties of these particular compounds are not disclosed in the Sakuma reference, the compounds existed and were isolated. The claims call the compounds "adjuvant[s]", however, using the term "adjuvant" does not convey a structural feature to the saponin compounds already known in the art. It is merely an intended use of the compounds. Therefore, the claims are anticipated by Sakuma.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 7-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sakuma (above) in view of Kensil (*Critical Reviews in Therapeutic Drug Carrier Systems*, 1996, 13(1/2):1-55). The claims are drawn to a vaccine preparation comprising the adjuvant of claim 1, comprising a saponin compound having a presenegenin skeleton substituted with a substituted or unsubstituted sugar residue at position 28, where the substituted sugar residue comprises an apiose residue as its substituent when the substituted sugar residue is tetra-substituted. Specifically, the vaccine preparation is administered intranasally or orally. The vaccine component comprises antigens from one or more pathogenic microorganisms such as influenza, pertussis and diphtheria, for example. The claims are only enabled for vaccines for certain microorganisms, not all the microorganisms listed in claim 9. However, in the interest of compact prosecution, the non-enabled vaccine microorganisms will be treated as immunogenic compositions.

The teachings of Sakuma are summarized above. Sakuma discloses the structures of onjisaponins A, B, E, F and G, but does not disclose a use for the compounds. However, Kensil reviews the use of saponins (triterpene glycosides from *Quillaja saponaria*) as vaccine adjuvants in inactivated influenza virus vaccines delivered intranasally (page 21, second full paragraph). Kensil also discloses the use of saponins as adjuvants with experimental HIV vaccines (page 22, second paragraph), various bacteria such as *E. coli* (page 24, line 1), *B. pertussis*, *Plasmodium yoelii*, *Toxoplasma gondii* (page 25, part C, "Parasitic Vaccines") and *Schistomona mansoni* (page 26, first full paragraph). It would have been obvious to use the onjisaponins of Sakuma as vaccine adjuvants. One would have been motivated to use them as adjuvants because saponin compounds are used as adjuvants; saponins and onjisaponins have the general saponin structure and have triterpene/triterpenoid structure. One of ordinary skill in the art would have known that saponins were useful as adjuvants, and would have had a reasonable expectation of success that the onjisaponins of Sakuma would have functioned similarly to saponins in general based on Kensil's review and the similarity of their structures. Therefore, the invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

8. No claim is allowed. Claims 1-9 are rejected.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stacy B. Chen whose telephone number is 571-272-0896. The examiner can normally be reached on M-F (7:00-4:30). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James C. Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Stacy B. Chen
October 25, 2004